ATTACHMENT 7

FEBRUARY 2000 FRENCH REPORT

Report

Revision of measures to minimising the risk of TSE transmission via blood products

February 2000

Report of the expert group convened under the aegis of the Agence Française de Sécurité Sanitaire des Produits de Santé (AFSSaPS) and the Etablissement Français du Sang (EFS)

Experts:
H. Agut, A. Alpérovitch, F. Barin, A.M. Couroucé, B. Danic, D. Dormont, M. Eloit, G. Folléa, C. Hannoun, F. Horaud, J. Leclerc and D. Sicard.

Representing the institutions:

Etablissement Français du Sang: G. Andreu, P. Hervé and D. Rebibo

Institut de Veille Sanitaire: I. Capek, J.C. Desenclos and J. Pillonel.

Etablissement Français des Greffes: B. Loty.

AFSSaPS: J.M. Alexandre, B. David, J.F Legras, N. Ounnoughene, E. Pouchol, F. Rossi, I. Sainte-Marie, C. Saura, J.H. Trouvin and P. Zorzi-Morre.

REPORT

Revision of measures to minimising the risk of TSE transmission via blood products
FEBRUARY 2000

Table of contents

List of abbreviations

AFS:	Agence Française du Sang
AFSSaPS:	Agence Française de Sécurité Sanitaire des Produits de Santé
BSE:	bovine spongiform encephalopathy ("mad cow disease")
BTC:	Blood transfusion centre
CJD:	Creutzfeldt-Jakob disease
DGDDI:	Direction Générale des Douanes et des Droits Indirects (Ministère de l'économie, des finances et de l'industrie)
EFS:	Etablissement Français du Sang
EMEA:	European Medicines Evaluation Agency
FDA:	Food and Drug Administration (USA)
GGSS:	Gerstmann-Sträussler-Scheinker syndrome
HBV:	hepatitis B virus
HCV:	hepatitis C virus
HIV:	human immunodeficiency virus
LBP:	labile blood products
LFB :	Laboratoire Français du Fractionnement et des Biotechnologies
MBM:	Meat and bone meal
MRM:	mechanically recovered meat
nv-CJD:	new-variant Creutzfeldt-Jakob disease
OFIVAL :	office national interprofessionnel des viandes, de l'élevage et de l'aviculture
PDP:	plasma-derived medicinal products
PrPres:	(or PrPsc), an abnormal form of the naturally occurring protein PrPc.
sp-CJD:	classical forms of Creutzfeldt-Jakob disease (sporadic, iatrogenic or familial)
TSE:	transmissible subacute spongiform encephalopathies
UK:	United Kingdom

Report

Revision of measures to minimising the risk of TSE transmission via blood products

February 2000

Introduction

As part of their technical and scientific surveillance activities, the AFSSaPS and AFS expert groups on safety met on 14 April 1999, 22 June 1999, 13 December 1999 and 4 February 2000 to review precautionary measures aimed at reducing the risk of transmission, via labile blood products (LBP) and plasma-derived medicinal products (PDP), of agents responsible for transmissible subacute spongiform encephalopathies (TSE) such as Creutzfeldt-Jakob disease (CJD). Currently, these precautionary measures are based on permanent exclusion from blood donation of persons with risk factors for TSE (1), namely a history of treatment with extracted pituitary hormones, extracted glucocerebrosidase of placental origin, dura mater transplants, neurosurgical investigations or operations, and a family history of TSE. Other, more broad-reaching measures, such as permanent exclusion of transfusion and transplant recipients since 1997 (2) and, since April 1998, leukodepletion[1] of labile cellular blood products, should further reduce the risk. Three contraindications to donation aimed at preventing classical TSEs have been clarified (history of ophthalmic surgery, history of tissue grafting of animal origin, and history of treatment involving medical devices in which products of bovine origin are used during the manufacturing process).

The main point considered during these meetings was the risk of transmission, via blood products, of new-variant CJD (nv-CJD), a disease first identified in the United Kingdom (UK) in 1995 (the first cases were officially declared in 1996), and which appears to result from transmission to humans of the agent responsible for bovine spongiform encephalopathy (BSE).

In early June 1999 the United States advisory board on TSE recommended to the FDA, in an attempt to reduce the potential risk of nv-CJD transmission by blood products, that persons having spent a total of at least 6 months in the United Kingdom between 1980 and 1996 should be permanently excluded from blood donation (3), and the French expert group proposed a transitory position on this question in June 1999. At that time the expert group considered that there was no public health emergency in France warranting exclusion of donors having stayed in the United Kingdom. This position was based on the fact that the risk of transmission of nv-CJD by blood products had not been clearly demonstrated, and that data were lacking on exposure to the BSE agent during stays in the United Kingdom or residence in France. Moreover, no data

[1] Leucodepletion: aseptic removal of the bulk of white cells from a labile blood product; the residual leukocyte content is less than 10^6 per cellular LBP unit.

were available on the likely impact of such exclusion measures on blood product availability. None the less, the expert group made a number of recommendations; the group's position was adopted and rendered public by the French health authorities on 18 August 1999 (4), following official announcement of the FDA's decision to exclude from blood donation all persons having spent more than 6 moths in the United Kingdom.

The present report summarises the technical and scientific data discussed by the group at the four meetings, and the group's opinion on the following points:

- scientific analysis of the risk of nv-CJD transmission via blood products,
- analysis of donor population exposure to the BSE agent, and likely efficacy of measures aimed at excluding donors having travelled to the United Kingdom,
- analysis of existing and available measures potentially reducing the risk of nv-CJD transmission via blood products,
- possible impact of exclusion of donors having stayed in the United Kingdom (blood supply, residual viral risks, etc.).

1- Scientific analysis of the risk of nv-CJD transmission via blood products

The following scientific data form the basis for the analysis of the risk of nv-CJD transmission via blood products:

- data on the tissue distribution of the pathological protein PrPres[2] (associated with infectivity) and the agent itself (potentially a prion), which point to the presence of the infectious agent in the periphery, and especially in blood,
- experimental data on the transmissibility of the disease by the IV route,
- epidemiological data on the risk of TSE transmission by blood products.

1-1 Peripheral distribution of nv-CJD

Infection by a TSE agent is diagnosed either by the detection of the pathological protein PrPres by physicochemical techniques (EIA, immunoblotting, electrophoresis, etc.) or by demonstrating infectivity by *in vivo* tests (bioassays) which can make use of various animal species and routes of inoculation.
These methods have been used to detect the agent responsible for "classical" (sporadic, familial and iatrogenic) forms of CJD (sp-CJD) and to detect the agent of nv-CJD.

1-1-1 Peripheral distribution of PrPres in nv-MCJ

- The main scientific argument pointing to a risk of nv-CJD transmission by blood is the detection of PrPres in lymphoid organs (tonsil, lymph node, appendix) of all 15 patients with nv-CJD so far tested, but never in lymphoid tissues (nodes, spleen, tonsil, immunocompetent cells) of 40 "control" patients with sp-CJD or other neurodegenerative diseases (5). Furthermore, in one case of nv-CJD, PrPres was detected in an appendectomy specimen obtained several months before clinical onset. This difference in tissue distribution between classical and new variant CJD might be linked to the route of inoculation of the infectious agent which, in the case of nv-CJD, would be the oral route, if one accepts the hypothesis that the initial source of infection is dietary (consumption of bovine products containing the BSE agent). This difference in tissue distribution can be interpreted in two ways: either PrPres is absent from lymphoid tissues of individuals with sp-CJD, or its level is below the detection limit (which corresponds to the amount of PrPres found in 10^4 LD50 in stabilised animal models). The first interpretation implies a real qualitative difference in the tissue distribution of the infectious agent between the two forms of CJD, with stronger peripheral tissue distribution in nv-CJD. In the second interpretation the quantitative difference in lymphoid tissue infectivity between the two forms of TSE might be less marked and, consequently, the risk of transmission by blood may be very similar. Neither interpretation currently seems more plausible than the other. However, both imply that the level of PrPres,

---

2 PrPres, or PrPsc, is an abnormal form of the natural protein PrPc; the latter is anchored to the surface of many mammalian cells. PrPc and PrPres have different resistance to treatment with proteinase K: endogenous PrPc is destroyed, while PrPres is partially resistant.

and consequently the potential infectivity of lymphoid and peripheral tissues, is higher in subjects with nv-CJD.

- A large prospective study aimed at anonymously screening the tonsil and appendix of British individuals for PrPres has been proposed. No results are available as yet.

- Bovine-bovine transmission tests are underway. Buffy coats[3] and homogenised lymphoid organs (nodes and spleens) from cows with physical signs of BSE have been injected intracerebrally (IC) into healthy cows (6). None of the inoculated animals has so far developed physical signs of the disease. However, considering the incubation period, which may be very long if the agent is only weakly present in the injected material, this does not rule out the possibility that the buffy coat and lymphoid organs may be infectious. These observations do, none the less, suggest that lymphoid organs would only be weakly infectious. It should be noted that results obtained in bovine cannot be directly extrapolated to other species: the infectivity of different tissues can vary from one species to another.

Available data indicate that the biological behaviour of the nv-CJD causative agent is different. They point to stronger peripheral distribution of the nv-CJD agent and a higher degree of infectivity compared with the sp-CJD agent. Not all data on classical CJD can therefore be extrapolated to nv-CJD.

1-1-2 Presence of PrPres in blood and its components

It should be noted that current data on the presence of TSE agents in blood are mainly based on experimental studies of infection by the agents responsible for scrapie, BSE and sp-CJD. Data on nv-CJD are awaited.

- A recent publication by P. Brown (7) showed that blood of mice infected by a human strain of GSSS[4] adapted to mice was infectious. For the first time, it was shown that the infectious titre in blood was lower during the incubation period than during the clinical phase of the disease and was insufficient to transmit the disease (cf. section 1.2).

- Whole blood appears to have low infectivity, as shown by the very small number of animals that developed the disease after intracerebral inoculation of whole blood in bioassays conducted to date (8). The infectivity associated with red cell and platelet concentrates appears to be very low or nil, and significantly below that of the buffy coat and plasma. Tests done so far suggest that the infectivity of blood is mainly associated with the buffy coat, which therefore appears to be the most infectious blood fraction. The infectivity of the buffy coat seems to be mainly linked to white cells. Thus, LBP leukodepletion appears likely to cause a marked reduction in the initial infectivity of blood and blood products. However, P. Brown showed that the low residual infectivity found in plasma after centrifugation might

---

[3] Buffy coat: layer containing white cells and platelets

[4] GSSS:Gerstmann-Sträussler-Scheinker syndrome

not be totally attributable to cell debris of lysed leukocytes. It would thus be necessary to determine, in conditions representative of routine leukodepletion in blood centres, the quantitative reduction in the infectivity of infected material, especially in the nv-CJD model (cf. section 3-1).

- Tests are underway in several laboratories to assess the infectivity of blood and blood components from patients with nv-CJD. However, these tests will be limited by the small number and limited volume of available samples.

- A new capillary electrophoresis method (9) was recently used to detect PrPres during the asymptomatic and clinical phases of the disease in animal whole blood (hamsters, sheep and wild ruminants) infected naturally or experimentally with a strain of the scrapie agent. However, the specificity of this new technique remains to be validated. It will also be necessary to calibrate the technique against bioassays based on models in which infectivity is known to correlate with the presence of PrPres. Moreover, application of this technique to blood samples from subjects with sporadic CJD and nv-CJD remains to be validated, especially regarding the detection limit, routine feasibility and predictive value in each form of CJD. If validated, this technique would not only serve as a diagnostic tool, but would also provide results more rapidly than bioassays on the infectivity of blood and its components, especially after leukodepletion and other treatments such as nanofiltration (cf. section 3-2).

Available data indicate the presence of PrPres and infectivity in blood during the asymptomatic and clinical phases of TSE. They suggest that infectivity is low and mainly associated with leukocytes, while the infectivity associated with red cells, platelets and plasma may be qualified as very low. Corresponding data on the agent responsible for nv-CJD are currently unavailable.

1-2 Experimental data on the transmissibility of the disease by the intravenous route.

If the suspected presence of the agent in blood is an argument in favour of a risk of disease transmission, it is inadequate to establish that nv-CJD is transmissible by blood products. Only direct tests can provide proof of transmission by the IV route. Available data can be summarised as follows:

- Many attempts have been made to transmit TSE intravenously with blood from infected animals. So far only some of these tests have shown, inconsistently, that the disease can be transmitted by injection of blood or blood components from animals infected experimentally with a strain of TSE (7, 8, 10).

- Tests of nv-CJD transmission by the peripheral or intracerebral route using blood from patients with nv-CJD are currently underway. These tests are being done in primates and transgenic mice (bovine PrP and human PrP). In primates, intracerebral and peripheral administration of blood from such subjects was done recently, and the results will only be available in several years. Tests involving transgenic mice are underway and the first interpretable results will be available no earlier than April 2000. The current absence of data showing transmission to inoculated animals does not mean that the risk of transmission can be ruled out, as these tests are not calibrated in terms of the infectious load (infectious dose/response ratio).

- The intracerebral route remains the most effective route of inoculation, before the intravenous and oral routes. The intravenous route is 7 to 10 times less efficient than the intracerebral route. However, the volumes of infectious material (even with a low infectious titre) that can be administered orally are far higher than the infectious doses that can be administered IC or IV (11). Thus, material with a low infectious titre administered orally in large amounts could transmit the infection, while this would not be the case with the IC or IV routes because of the small volumes involved.

Ongoing investigations on nv-CJD transmission by blood do not allow conclusions to be drawn on the existence or degree of the risk.

1-3 Epidemiological data on the risk of TSE transmission via blood products

The following factors must be taken into account when analysing the risk of transmission of the agent responsible for TSE by blood products. Note that most available data concern sp-CJD.

- American and English surveys of recipients of LBP and PDP prepared from donations by subjects who subsequently developed sp-CJD have failed to detect cases of CJD transmission (12a, 12b).

- There has been no rise in the number of cases of CJD in patient populations (e.g. haemophiliacs) who receive large amounts of LBP and PDP. More precise studies, including neuropathologic examination of haemophiliacs with neurological diseases, have failed to identify cases of CJD (13). It is noteworthy that in the last 15 or 20 years, while the use of blood products has increased markedly, the incidence of CJD does not seem to have changed, either in the general population or in patients treated with blood products. These data have limited implications, however, given the small group sizes and the level of risk which, in principle, is low.

- Epidemiological case-control studies done in Europe (14) and Australia (15) on a large number of cases of CJD have revealed no risk linked to blood products.

- As regards cases of nv-CJD described in the United Kingdom, France and Ireland, it appears that exposure to a risk factor by the IV route may be excluded, as no particular history of transfusion has been found.

- Six of the 52 cases of nv-CJD observed in the United Kingdom as of 31 December 1999 involved blood donors. A survey of identified recipients who received LBP prepared from these subjects' donations has so far shown no signs compatible with nv-CJD. It should however be noted that these data are limited in terms of the sample size and follow-up period.

- Given the long incubation period, it can be considered that all human cases of nv-CJD observed so far correspond to cases of primary infection by the bovine agent. It is too early to observe possible cases of secondary infection due to human-human transmission (mother-child, nosocomial, iatrogenic, etc.).

Epidemiological data show no link between blood product use and TSE. These data, which have limited value given the small group sizes, do not formally exclude a small risk, especially for nv-CJD, given the short available follow-up period.

1-4 Conclusion on the scientific analysis of the risk of nv-CJD transmission via blood-products

As regards "classical" CJD, the experts consider that experimental and epidemiological data, and available follow-up data, suggest that the risk is very low and possibly nil. Indeed, many data now converge towards the conclusion that observation of a case of sp-CJD transmission by blood products is highly improbable (7). Current precautionary measures (exclusion of blood donors, withdrawal of batches of PDP, information for prescribers) should thus be revisited.

In contrast, a risk of nv-CJD transmission by blood products is compatible with the presence of the infectious agent in lymphoid tissues (the stronger peripheral distribution potentially reflecting a higher level of infectivity). However, current experimental and epidemiological data fail to demonstrate transmission by blood products (blood or infectious tissue, and by the intravenous route). Ongoing studies of nv-CJD transmission by blood have not yet shown whether the risk exists: it is therefore a potential risk that must be taken into account by maintaining scientific surveillance together with strict epidemiological monitoring.

2- Analysis of blood donor population exposure to the BSE agent

To evaluate the benefit of deferral of blood donors having been exposed to the BSE agent, one must take into account current data on the mode of transmission of this agent to humans, together with risk factors and the period of population exposure, and place in perspective the different sources of blood donor exposure to this agent.

2-1 Mode of transmission of the BSE agent to humans and factors of exposure

2-1-1 Experimental evidence of transmission of the BSE agent to humans

The link between the causal agent of nv-CJD in humans and the BSE agent in cows is based on animal experiments. For example, a recent study by S. Prusiner's team (16) showed that intracerebral injection of brain extracts from patients with nv-CJD to transgenic mice expressing human PrP can lead to the disease, and that the incubation period is even shorter in transgenic mice expressing bovine PrP; in this latter model the neuropathologic lesions were identical to those found in patients with nv-CJD. This finding, combined with previous data such as biochemical typing (17) and biological strain properties (18), supports the bovine origin of the nv-CJD agent found in humans.

2-1-2 Epidemiology of nv-CJD worldwide: trends and risk factors

According to the experimental data outlined above, it seems that the species barrier could, to a certain extent, reduce the transmission of the BSE agent to humans. This relative human resistance to transmission of the bovine agent could translate into a very long incubation period, which would mean that the 55 cases of nv-CJD so far observed worldwide (52 in the United Kingdom, 1 in Ireland, 2 in France) would be of "rapid onset", preceding the bulk of cases that would have longer incubation periods and that have not yet occurred. Other suspected cases are being investigated both in the United Kingdom and in France.

In the United Kingdom, data published in late 1998 were compatible with a rise in the incidence of nv-CJD (the yearly incidence was 17 in 1998, compared to 10 cases each in 1996 and 1997). Only 11 cases were recorded in 1999. At this stage, given the very small numbers of cases, it is very difficult to draw firm conclusions as to epidemiological trends in the disease.
No factors of dietary exposure capable of explaining the infection have yet been identified in case-control studies done in the United Kingdom, partly because of the small number of cases and partly because the controls had a similar diet to the subjects with nv-CJD.
Thus, it has still not been formally established that transmission of this agent is due to ingestion of infectious bovine tissues or, if this is the case, that food is the only factor of exposure to BSE.
The age of subjects with nv-CJD ranges from 14 to 51 years. Current epidemiological data, including those on cases involving very young subjects do not allow the date of exposure or the duration of incubation to be determined. The young age at clinical onset of nv-CJD (mean 28 years) remains to be explained: a cofactor linked to lifestyle or dietary habits, or a susceptibility factor linked to age, might be necessary for transmission.

Currently, the team headed by R. Will, which is responsible for epidemiosurveillance of this new disease in the United Kingdom, considers that the following risk factors have so far been identified: i) residence in the United Kingdom, ii) Met/Met homozygosity at codon 129 of the PrP gene, and iii) age. The team currently favours the hypothesis whereby mechanically recovered meat (MRM) was a preferential vehicle for dietary transmission of this agent.
Thus, current epidemiological data give no meaningful indications, apart from exposure to a poorly identified agent (nature of the infectious material, mode of administration, single or repeated infectious doses?), with an unknown exposure period and duration of incubation.

The first case of nv-CJD in the Republic of Ireland was reported in June 1999 (19). This country has had 377 cumulative cases of BSE since 1989, a total similar to that of Portugal and Switzerland. According to information provided by the Irish health authorities, this case of nv-CJD involves a woman of 30-40 years of age who had lived in England for a long time. Thus, this case is not particularly surprising, given the proximity of Ireland and the United Kingdom (visits) and exposure to bovine products imported from the United Kingdom. This Irish case has not yet been confirmed (according to the definitions of "confirmed" and "probable" cases used by the European nv-CJD epidemiosurveillance team).

In France, two cases have been officially declared, one in 1996 and one in 1999. These two patients had no particular exposure factors and had not stayed in the United Kingdom. It should be recalled that, according to data published by the United Kingdom (HM Customs and Excise), France was a leading European importer of bovine products (all product types such as cattle, carcasses, offal and meat and bone meal –MBM-) during the period 1980-1996. Thus, if transmission of the agent indeed occurs via the food chain, these two cases would reveal endogenous global exposure of the French population linked to consumption of British bovine products before the embargo.

No other cases of nv-CJD (suspected or confirmed) have to date been declared in other European countries, which all now have TSE monitoring systems of similarly quality.

Finally, it is important to note that the epidemiological characteristics of TSE (all forms) have not appreciably evolved in recent years in Europe, suggesting that the cases of nv-CJD in the countries concerned represent well-identified clusters.

2-2 Period of population exposure to the BSE hazard

The experts identified two periods of exposure to the BSE agent. The first is from 1980 to 1989 and the second from 1990 to 1996. 1980 corresponds to the probable beginning of the development of the disease in cows. In the "meat and bone meal hypothesis", 1980 marks the possible introduction into the food chain of cows in the preclinical incubation phase of the disease. 1989 is the date at which the first preventive measures targeting the food chain were decided on in the United Kingdom (especially specified ban offal).

Further preventive measures were taken between 1990 and 1996 in France, the United Kingdom and Europe (ban of offal and MBM, etc.). 1996 corresponds to the beginning of the embargo on

British bovine meat in France and the date at which the British authorities considered that measures in place were sufficient to stop the development of BSE and to ensure that no infected bovine material entered the British food chain.
Consequently, the period of human dietary exposure to the risk of BSE transmission identified by experts is between 1 January 1980 and 31 December 1996, even if there was no doubt a fall in the risk of exposure to the BSE agent as early as 1990, after adoption of a series of protective measures. The period most at risk is situated between 1985 and 1990, a period when the number of cattle with BSE was high, and when specified risk offal had not yet been removed from the food chain.

2-3 Estimation of population exposure to the BSE agent between 1980 and 1996

The mechanism of transmission of the BSE agent to humans is still not known. The dietary hypothesis remains the most probable, but other potential modes of transmission on which no scientific data are available should not be overlooked. Despite these uncertainties, epidemiological data on nv-CJD and exposure to the BSE risk are now relatively coherent. The period of exposure to the dietary risk, not only in the United Kingdom but also in France (and other European countries importing British bovine products) is 1980-1996, with a maximal risk between 1985 and 1990.
Before envisaging exclusion from blood donation of persons exposed to the BSE agent during stays in the United Kingdom, it is necessary to estimate, for the same period, not only the risk of exposure during such stays in the United Kingdom but also the risk of exposure resulting from residence in France.
For this purpose the experts considered that the two main sources of exposure were stays in the United Kingdom between 1980 and 1996 and consumption of imported British bovine products in France during the same period.

2-3-1 Donor exposure during stays in the United Kingdom

As recommended by the experts after the meeting of June 1999, a survey was conducted among ten blood transfusion centres (BTC)[5] located throughout France to measure blood donor exposure to the BSE agent during stays in the United Kingdom. The survey was co-ordinated by G. Folléa, after discussion of the protocol by C. Berr and A. Alpérovitch (INSERM U 360), AFS and AFSSaPS. The survey was based on a self-questionnaire given to each person who presented to donate blood during the week from 18 to 24 October 1999. The following data were collected on each candidate donor: sex, age, donor status (first-time or repeat donor), the type of donation, the number of donations in the previous 2 years, and the cumulative time spent in the United Kingdom during two periods (1980-1989 and 1990-1996).

The main results were the following:

- The 17,596 donors surveyed were not fully representative of the national donor population (in 1998), especially as regards donor status and sex: the proportion of first-time donors was

[5] ETS Alpes-Provence, ETS APHP, ETS Bretagne-Est, ETS Bourgogne-Franche-Comté, ETS Haute Savoie, ETS Loire Atlantique Vendée, ETS Nord Pas de Calais, ETS Ouest Francilien, ETS Pyrénées Garonne et ETS Strasbourg.

lower (12.6% versus 26.8%) and the proportion of males higher (57.5% versus 53.5%). However, the levels observed in the survey were very close when corrected for sex, age, and donor status.

- 20.5% of donors had spent at least one day in the United Kingdom between 1980 and 1989, and 25.2% between 1990 and 1996, i.e. a cumulative total of 34.6% for the period 1980–1996,

- the factor most strongly linked to the frequency of stays was age: 55.3% of donors between 18 and 29 years had travelled to the United Kingdom, compared to 28 to 29% of donors between 30 and 49 years and 23.2% of donors over 50 years,

- there was wide variability in the responses among the different BTCs: 17% of donors in Franche Comté-Bourgogne had travelled to the United Kingdom, compared to more than 40% of those in Rennes and Lille, and more than 50% of those in the Paris region (100% in Versailles).

These data can be used to estimate the cumulative exposure of the blood donor population during stays in the United Kingdom.
If we consider that a one-day stay in the United Kingdom corresponds to an arbitrary unit risk of one person-day (PD), and that the risk is cumulative, a 10-day stay represents a risk of 10 person-days, and a 30-day stay by one person represents an equivalent cumulative risk to 30 one-day stays by different individuals.

On this basis (identical to that used in the USA), A. Alpérovitch calculated the curve of cumulative exposure of the surveyed donor population, and the relative contribution of each length of stay (see table below).

Cumulative stay	Percentage of donors concerned	% of exposure linked to stays in the United Kingdom
≥ 1 day	33.28%	100%
≥ 7 days	20.37%	96.85%
≥ 15 days	11.38%	91.46%
≥ 1 month	5.58%	83.66%
≥ 3 months	2.28%	70.82%
≥ 6 months	1.29%	63.04%
≥ 1 year	0.71%	54.33%
≥ 2 years	0.39%	43.51%
≥ 5 years	0.12%	22.04%

On the basis of these exposure data, if cumulative exposure to the risk of BSE, linked to stays in the United Kingdom, is to be reduced by 90%, it would be necessary to exclude all donors having spent more than 15 days in the United Kingdom, i.e. approximately 11% of donors.

In the United States, this criterion of 90% of the total risk exposure, which is that adopted by the FDA (cf. 4-1), entails the exclusion of 2.2% of donors in the USA, as it only concerns the donor population having spent more than 6 months in the United Kingdom. In other terms, given the travel habits of the American donors, donors spending more than 6 months in the United Kingdom account for 90% of the total exposure of American donors to the BSE hazard.

2-3-2 Exposure of donors to the BSE hazard in France

As stated above, after estimating the exposure of French donors to the BSE hazard during stays in the United Kingdom, it is also necessary to estimate exposure to the BSE hazard during residence in France, linked to the consumption of imported British bovine products.
Several hypotheses are required for this estimation.

2-3-2-A- Hypotheses

This estimation of exposure to the BSE hazard in France is based on the following hypotheses:

Hypothesis 1: the risk of infection by nv-CJD is linked to the consumption of British bovine products containing the BSE agent during the period 1980-1996, in the absence of other valid hypotheses on factors of exposure,

Hypothesis 2: the risk of exposure to BSE linked to consumption of British bovine products in the United Kingdom and the risk linked to the consumption of British bovine products in France are considered equivalent. This hypothesis does not take into account possible differences in the nature of British bovine products, especially some types of offal, entering the food chains in the United Kingdom and France, or those possibly resulting from differences in modes of slaughter and meat preparation in the two countries, or differences in the age distribution of the animals consumed.

Hypothesis 3: the risk linked to consumption of French meat infected by the BSE agent is not taken into account because i) it is not currently quantifiable, and ii) its contribution is probably limited compared with the risk linked to consumption in France of British bovine products between 1980 and 1996. This hypothesis underestimates exposure to BSE in France and consequently overestimates exposure linked to stays in the United Kingdom.

Hypothesis 4: the risk linked to consumption of imported British meat during stays in other foreign countries is considered negligible, considering that France was the principal importer of bovine products from the United Kingdom. This hypothesis does not take into account the nature and quality of British bovine products imported by the different countries, which might influence exposure to the risk. Exposure to BSE of donors having visited countries outside France and the United Kingdom during this period is considered negligible. In other words, stays in other European countries are considered to carry a negligible risk.

Hypothesis 5: the risk that a given individual has of being infected by the BSE agent, and therefore being potentially capable of transmitting it, is proportional:

- to the duration of exposure (in days)

- to the level of exposure, which is itself proportional to the amount of British bovine products consumed. Depending on this level, a person exposed for one day in the United Kingdom will have a risk **ruk** of being infected, while a person exposed in France will have a risk **rf**.

Hypothesis 6: the ratio of exposure in France and the United Kingdom was constant throughout the period considered. This hypothesis and the previous hypotheses imply that the ratio of the risks of infection by the BSE agent for a given duration of exposure was also constant during the period considered.

2-3-2-B- Method used to estimate the risk linked to stays by donors in the United Kingdom relative to the risk linked to residence in France

Based on all the above hypotheses the risk was calculated as follows:

- donor exposure was estimated in person-days. The total duration of exposure being 6 205 days (17 years) and the number of donors who replied to the questionnaire being 16 787, the total number of person-days (TPD) is therefore 104,163,335 PD.

- this number can be divided into two parts, corresponding to exposure in the United Kingdom and exposure in France. Thus, a donor who spent 3 months in the United Kingdom was exposed:
  - to a risk of infection **ruk** for 90 days
  - to a risk of infection **rf** for 6,205 - 90 days, i.e. 6,115 days
  - This donor's risk of infection is therefore: 6,115 **rf** + 90 **ruk**

As, in the donor sample studied (N = **16,787**), stays in the United Kingdom totalled 275,434 person-days (PD**uk**), and as the total number of person-days (TPD) is 104,163,335 one can express the total risk TR as:

$$TR = (TPD - PD\mathbf{uk})\,\mathbf{rf} + (PD\mathbf{uk}.\ \mathbf{ruk})$$

As **rf** is a fraction of **ruk** (**rf** = a. **ruk**), the part of the total risk linked to donor exposure in the United Kingdom can be calculated as follows:

$$\boxed{(PD\mathbf{uk}.\ \mathbf{ruk})/TR = PD\mathbf{uk}/[a.(TPD - PD\mathbf{uk}) + PD\mathbf{uk}]}$$

Two approaches can be used to determine the value of **rf** to be used in the equation:

- **Using quantities of British bovine products imported by France**

Globally concordant data from French sources (OFIVAL[6], DGDDI[7]) and British sources (HM Customs and Excise) indicate that approximately 5-10% of the bovine meat consumed in France

[6] OFIVAL: office national interprofessionnel des viandes, de l'élevage et de l'aviculture.

[7] DGDDI: direction générale des douanes et des droits indirects (Ministère de l'économie, des finances et de l'industrie)

during the period considered was imported from the United Kingdom. For the analysis of comparative levels of exposure in France and the United Kingdom, it would be useful to know the amount of British bovine products consumed in France, as a fraction of consumption of the same products in the United Kingdom. The calculations are based on the hypothesis that mean per capita bovine product consumption is the same in France as in the United Kingdom and did not change during the period concerned. On the basis of these data, two values for **rf** can be proposed:

- **rf** = 0.05 **ruk**, based on the lower estimate of British bovine product consumption in France between 1980 and 1996
  In this scenario, the risk linked to donor exposure during stays in the United Kingdom (PD**uk**. **ruk**)/TR represents 5% of the total risk (France + stays in the United Kingdom). Thus, if one excluded all donors having spent at least one day in the United Kingdom, i.e. 33% of donors, the reduction in the risk would be 5% and the residual risk of exposure to the BSE agent associated with residence in France would be 95% of the total estimated exposure of French donors.

- **rf** = 0.10 **ruk**, using the upper estimate of British bovine product consumption in France between 1980 and 1996
  In this scenario, and using the same method of calculation as above, if one excluded all donors having spent at least one day in the United Kingdom the reduction in the risk would be 2.6% and the residual risk would be 97.4%.

By using these lower and upper estimates, and by taking into account different durations of stays in the United Kingdom as criteria for donor exclusion, the reduction in total exposure to the BSE hazard can be summarised as follows:

Residual risk	Exclusion ≥ 1 day	Exclusion ≥ 7 days	Exclusion ≥ 15 days	Exclusion ≥ 1 month	Exclusion ≥ 3 months	Exclusion ≥ 6 months	Exclusion ≥ 1 year
% of donors excluded	33.3%	20.4%	11.4%	5.6%	2.3%	1.3%	0.7%
rf = 0.1 **ruk**	97.4%	97.5%	97.6%	97.8%	98.2%	98.4%	98.6%
rf = 0.05 **ruk**	95.0%	95.1%	95.4%	95.8%	96.5%	96.8%	97.3%

- **Using the incidence of nv-CJD in France and the United Kingdom**

If one calculates the risks (**rf** and **ruk**) according to the incidence rate of nv-CJD in the British and French populations and the asymptomatic phase of the disease during which a donor can give blood, and given that the number of inhabitants in the two countries is appreciably the same (60 million) and that cases were observed during the same period (1996-1999), one obtains:

$r_{uk} = I_{uk} . AP$ and $r_f = I_f . AP$, where
I_{uk} and I_f = incidence rate of nv-CJD in the United Kingdom and in France respectively,
PA = asymptomatic phase of the disease during which the donor may give blood.

Then $r_f / r_{uk} = I_f / I_{uk} = 2/52$ and $r_f = 0.04\ r_{uk}$

This result is close to $r_f = 0.05$, which is the lower estimate of the proportion of British bovine products consumed in France between 1980 and 1996.

Thus, the hypothesis which appears most relevant is $r_f = 0.05\ r_{uk}$, as it is in keeping with available quantitative data on imports (on average, 6% of bovine products consumed in France between 1980 and 1996 were of British origin) and incidence data on nv-CJD in France and the United Kingdom.

Whatever the scenario, these estimates show the limited part of donor exposure to the BSE agent represented by donor stays in the United Kingdom, i.e. approximately 5% of total exposure. This limited impact on global exposure is explained by the fact that the consumption of British bovine products concerned the entire French population throughout the period considered (1980-1996), even if the exposure level was 20 times lower than in the United Kingdom ($r_f = 0.05\ r_{uk}$***), while stays in the United Kingdom concerned only a third of the donor population and involved far shorter periods.***

2-4 Discussion

- **Consideration of exposure in France to the BSE agent due to consumption of bovine products imported from the United Kingdom in the analysis of exposure**

The first two cases of nv-CJD reported in France involved subjects who had not travelled to the United Kingdom, pointing to the existence of other sources of exposure to the BSE agent. British data (HM Customs and Excise, see above) show that France was the principal importer of British bovine products during the period concerned. This is also in keeping with the hypothesis of dietary exposure in France via imported bovine products, in the current absence of cases of nv-CJD in other European countries.

- **Discussion of the hypotheses used to estimate exposure to the BSE agent**

The most critical hypothesis is that linking the risk of exposure in France to the risk of exposure in the United Kingdom ($r_f = 0.05\ r_{uk}$). This link is based on quantitative data on importation of British bovine products and global consumption of bovine products in France throughout the period concerned.
Indeed, these hypotheses do not take into account factors potentially influencing exposure to BSE, which may have been different in France and the United Kingdom, such as the

consumption of bovine products, the nature of the products consumed, slaughter, and the age of the animals (cf. hypothesis 2). Similarly, they do not take into account a possible change in the risk ratio between France and the United Kingdom during the period 1990-1996 resulting from human protection measures applied since 1989 (prohibition of consumption and importation of specified risk offal in the United Kingdom and France, specific quality criteria for veal imported from the United Kingdom, quality of meat and carcasses imported from the United Kingdom, and reinforcement of epidemiosurveillance, controls and repressive measures).

However, while it is likely that these measures contributed to reducing exposure to the BSE hazard, data on the quality of imported products cannot be used to estimate the risk differential between the consumption of British bovine products in the United Kingdom and in France during the period 1990-1996. Currently available qualitative data, although limited, show that some MRM was prepared in France from raw materials of British origin. A detailed analysis of qualitative consumption of bovine products in France and the United Kingdom and complementary data on BSE transmission to humans would be needed for a real assessment of population exposure to BSE and to develop more precise hypotheses.

Even if, for example, the risk of exposure was 100 times lower in France (**rf** = 0.01 **ruk**), donor exposure to BSE during stays in the United Kingdom would represent 21% of total exposure to the BSE hazard during the period 1980-1996. By assuming exposure factors of 0.05 for the period 1980-1989 and 0.01 for 1990-1996, donor exposure to BSE during stays in the United Kingdom would represent approximately 7% of total exposure. These figures show that, even in extreme scenarios, the proportion of the risk linked to stays in the United Kingdom remains limited.

Finally, it must be stressed that even if it does not take into account these qualitative factors, the risk ratio of 0.05 is in keeping with the current epidemiology of nv-CJD in the two countries. If there is a bias, it cannot be estimated on the basis of current data. Moreover, if British bovine products imported to France were less at risk than those consumed in the United Kingdom, driving the risk ratio down to 0.01 or 0.001, the fact that cases have been declared in France would suggest the existence of a source of exposure other than the consumption of British bovine products in France and stays in the United Kingdom.

Consequently, the experts consider the ratio of 0.05 to be coherent and a reasonable estimate on which to base further deliberations.

- **Discussions on the efficacy of excluding donors having spent long periods in the United Kingdom**

Current data on exposure to the BSE agent in France suggest that exclusion of donors who travelled in the United Kingdom would only marginally reduce global donor exposure to BSE (see table above), and consequently would have a limited impact on the potential risk of nv-CJD transmission by blood products.

Nevertheless, some experts raised the question of excluding donors having spent long periods in the United Kingdom.

One of the hypotheses used to estimate global exposure to BSE in France is that a stay in the United Kingdom during the period considered would lead to a rise in exposure that was proportional to the duration of the stay. Thus, individuals having spent long periods in the United Kingdom would have a higher individual risk than subjects not having travelled to the United Kingdom.

For example, taking the ratio of 0.05 between exposure in France and the United Kingdom, exposure of a person who spent a year in the United Kingdom (expressed in person-days) would be increased two-fold compared with an individual never having spent in the United Kingdom. Exclusion of donors having spent more than a year in the United Kingdom would reduce by only 2.7% the global exposure of the donor population. After a stay of 5 years, exposure would be multiplied by a factor of about 7, and exclusion of persons having spent more than 5 years in the United Kingdom would reduce global donor exposure by only 1.1%. In the extreme scenario in which the risk ratio is 0.01, exposure of persons having spent at least 1 year in the United Kingdom would be multiplied by at least 7, and exclusion of these donors would reduce the exposure of the donor population by 12%.
The question is whether or not these over-exposed individuals should be excluded from donation. Even if it is possible to estimate these individuals' over-exposure in person-days, it is not possible to determine whether this over-exposure is significant in terms of the probability of carrying the nv-CJD agent or transmitting it. Indeed, data on BSE transmission to humans are currently inadequate for individual risk analyses or to correlate a certain duration of stay in the United Kingdom with a rise in the probability that a given individual will develop the disease. In particular, it is not known if transmission occurs after repeated exposure or after a single infectious dose (it should be recalled that almost all experimental data are based on single doses).

Contrary to factors of exposure to HIV or HCV screened for in blood donors in the setting of an individual risk analysis based on epidemiological data, even if the risk factor "stays in the United Kingdom" is associated with a rise in exposure, it does not correlate, at the epidemiological level, with a significant rise in the risk of developing nv-CJD. Thus, during the period at risk, millions of foreigners, mainly from other European countries, stayed in the United Kingdom. The current absence of cases of nv-CJD among these travellers must be taken into account in assessing the risk of nv-CJD linked to stays in the United Kingdom. In contrast, the risk factor "residence in the United Kingdom" correlates with the risk of developing nv-CJD. The duration of the stay is one of the factors that distinguishes residence from stays in the United Kingdom, although it is not possible to determine a "cut-off" value in terms of time spent, or factors of exposure in the United Kingdom that are independent of the duration of the stay and carry a significant excess risk.

Moreover, it must be recalled that despite uncertainties on the expected number of cases of nv-CJD in the United Kingdom, current data suggest that the risk of infection linked to exposure throughout the period at risk is very low. Even if there were 1,000 cases of nv-CJD in the United

Kingdom in years to come, the risk denominator would be expressed in billions of person-days (several tens of millions of people each exposed for several thousand days). The risk of nv-CJD corresponding to a few months spent in the United Kingdom is obviously even lower. Today, cases of nv-CJD have only occurred in countries in which the overall population has been exposed to the BSE agent. Changes in epidemiological data may call this analysis into question and must be watched closely.

In conclusion, the experts consider that stays in the United Kingdom, and especially long stays, are a source of over-exposure to the BSE hazard. Nevertheless, on the basis of available epidemiological data, this over-exposure to the BSE hazard linked to long stays in the United Kingdom cannot be correlated with a significant rise in the individual risk of developing nv-CJD. Available data are inadequate to define a duration beyond which over-exposure may become significant for a given individual, or to consider that the over-exposure due to long stays in the United Kingdom is significant in terms of the risk for the community.

3- Analysis of methods potentially reducing the risk of nv-CJD transmission by blood products

Given the overall exposure to the BSE hazard of the blood donor population and the fact that a donor exclusion measure would, at best, have a limited impact on overall exposure, other measures to reduce the potential risk of nv-CJD transmission by blood products, some of which are already in place, must be assessed. Currently, in the absence of validated tools for the detection of the infectious agent in blood, these measures are based on processes involved in blood product preparation.
This section examines existing and available techniques which are potentially capable of reducing the infectious load, if present, in blood and blood components.

3-1 Labile blood products

3-1-1 EFS assessment of the current situation

Leukodepletion of all cellular LBP (namely red cell concentrates and platelets) has been in place in France since April 1998.
Two methods are currently used: whole-blood filtration and cell-concentrate filtration.
In both methods the reduction in the number of leukocytes (mandatory limit: $\leq 10^6$ residual leukocytes/unit transfused) in cellular LBP is at least 3 logs compared with the initial content (about 3×10^9 leukocytes/unit).

As regards plasma, one must distinguish between:

- apheresis plasma (source plasma), mainly prepared for direct therapeutic use, for which no filtration devices have so far been available: the residual leukocyte content of apheresis plasma is between 10^6 and 10^8 per 600-ml unit.

- plasma derived from whole blood (recovered plasma) and destined for fractionation, of which:
  - approximately 50% is derived from whole-blood filtration and has a mean residual leukocyte content of 3×10^4 per 250-ml bag,
  - approximately 50% is derived from whole blood separated without filtration and has a mean residual leukocyte content of 10^7 per 250-ml bag.

In early 1998, the Laboratoire Français du Fractionnement et des Biotechnologies (LFB) and AFS defined a joint action program aimed at leukodepletion of all plasma units. Three devices have been tested for filtration of plasma obtained by whole blood separation. Other devices are to be tested in 2000, of which at least two are designed for filtration of apheresis plasma. The estimated time required for the assessment and registration by AFSSaPS of the plasma obtained by means of these devices, is one year (i.e. late 2000).

It should be noted that the current exclusive use of aphaeresis plasma for direct therapeutic use is aimed at minimising the number of donors to which each patient is exposed. Leukodepleted plasma, derived from filtered whole blood with a mean leukocyte content of $3x10^4$ /unit (see above), is currently available but more donors would be required to treat one patient.

3-1-2 Analysis of the impact of LBP leukodepletion on the potential risk

The infectivity of blood is thought to be mainly associated with leukocyte component (cf. section 1-1-2); as a result, leukodepletion of cellular LBP would be an effective means of reducing the potential risk of TSE transmission. Nevertheless, the quantitative reduction in infectivity potentially present in blood provided by leukodepletion has not been assessed in conditions representative of routine leukodepletion of blood products.

On the basis of current data, the experts consider that LBP leukodepletion would certainly be effective in reducing infectivity, even if mononuclear cells, which are recognised as being associated with infectivity, are not the principal cells eliminated by filtration (the residual leukocyte population after filtration is mainly composed of T lymphocytes).

EFS has contacted the CEA neurovirology service to conduct validation studies. The difficulty now is that, to conduct this type of study, it would be necessary to obtain blood from a person with nv-CJD, which raises ethical problems. Test using blood of mice infected by the GSSS strain would also pose a problem, owing to the low infectious titre (which would make it difficult to detect any reduction) and the fact that mouse blood does not have the same behaviour as human blood (cell size and rheology) in leukodepletion filters. These are major methodological difficulties. It will be necessary to await the results of ongoing studies in animal models to detect the infectivity associated with blood from subjects with nv-CJD. These results will help to optimise the methodology of studies aimed at evaluating the contribution of leukodepletion to the reduction in blood infectivity (if the nv-CJD agent is indeed present in blood).

3-2 Plasma-derived medicinal products

3-2-1 Review of available data

As regards plasma-derived medicinal products (PDP), i.e. protein fractions specifically fractionated from plasma pools, the experts discussed safety from the point of view of the risk linked to the presence of human TSE agents in the starting plasma:

- Given the relative fragility of plasma proteins with therapeutic value and the high degree of resistance of TSE agents to inactivation procedures (alkaline treatment, heat, etc.), it appears difficult, in the current state of protein purification techniques, to envisage a way of inactivating these agents if they are present in the starting material.

- In contrast, it may be possible to eliminate these agents by means of partition or filtration methods. However, it will be necessary to assess the capacity of these methods to eliminate the TSE agent(s). A number of relevant studies have already been conducted, and their results have been published or reported at conferences. A global analysis of these initial results (20, 21) shows that:

- fractionation steps involving centrifugation followed by precipitation or filtration can reduce the titre of an added infectious agent by approximately 1 to 3 logs.
- chromatography steps are also able to reduce the load of infectious agent. The reduction factor is largely dependent on the type of chromatography used and the material chromatographed.
- low-porosity filters (nanofiltration) also reduce the load of infectious agent. There appears to be a close relationship between the pore size of the filter and the reduction factor. Filters with a pore size of 15 nm, such as Planova, seem to have satisfactory effectiveness. The aggregation status of the infectious agent also influences the effectiveness of nanofiltration.

All these results are preliminary and difficult to interpret, for the following reasons:

- The nature of the agent added (spiked): reduction factors are dependent on the type of infectious material added (brain homogenate, fibrillar protein concentrate, blood from subjects infected by TSE agents, etc.). The results must therefore be carefully interpreted.

- The method used to detect and follow the fate of the agent during the elimination step. Currently, there are two possible approaches:

  i) titration of the agent by means of an animal infectivity test (bioassay). This method is the most valid, but results are available after several months, only when the bioassay is interpretable (depending on the incubation period in the animal model and the infectious titre)

  ii) quantification of PrPres protein by methods such as western blot (WB) and other immunodetection methods (EIA, Delfia, etc.). These methods are more rapid but provide no information on infectivity. The results provided by these methods must thus be correlated with bioassay data first. Reductions in the load of infectious agent shown by WB have already been validated and correlated with bioassay data. The use of biochemical PrPres detection techniques is therefore feasible, especially for an initial estimation and analysis of a fractionation process, in order to identify steps that contribute significantly to elimination and that can subsequently be validated by a bioassay.

As in viral validation studies, each fractionation process should be subject to a specific validation study of its capacity to eliminate TSE agents. The results presented here only provide global indications of the overall capacity of fractionation processes considered together, because they all use similar fractionation and chromatography steps, with minor technical variations.

3-2-2 Analysis of the impact of PDP manufacturing processes on the potential risk

Despite the technical difficulties listed above, the experts consider that it is reasonable to conclude that fractionation techniques contribute to eliminating TSE agents potentially present in the starting plasma (plasma pools). Currently, based on the assumption that the initial infectious load is probably small (cf. 1-1-1), the effectiveness of partition steps seems to be sufficient to eliminate the potential initial load.

The experts nevertheless recommend that studies be continued to determine the precise capacity of each process to reduce the infectivity of each product. This reduction capacity will have to be interpreted according to data on initial infectivity as knowledge in this field progresses. According to the estimations of the initial load and the capacity of the processes to reduce infectivity, recommendations on the addition of an elimination step (e.g. nanofiltration) may be envisaged.

As regards PDP prepared by LFB, in addition to elimination steps provided by the different processes currently in use, it is necessary to underline that the starting plasma is itself partly leukodepleted (cf. 3-1-1), improving the quality of the starting material as regards the risk of TSE.

3-3 Conclusion on the contribution of existing and available techniques reducing the potential risk of nv-CJD transmission by blood products

The analysis of the processes used for the preparation of both LBP and PDP shows that they contribute significantly to reducing the potential risk of nv-CJD transmission by blood products, even if the following steps must be taken:

- extension of leukodepletion to all plasma products, especially those derived from plasmapheresis,
- validation of the reduction in the potential infectious load of LBP by leukodepletion in conditions representative of their routine preparation, if possible with nv-CJD
- pursuit of validation work on steps potentially reducing the infectious load during the fractionation of PDP and, when warranted, introduction of nanofiltration of purified protein solutions.

4- Position of other countries and institutions

4-1 State of the decision-making process in other countries

In the United States, the FDA announced on 17 August 1999 a decision to exclude from donation all persons having spent more than 6 months in the United Kingdom between 1980 and 1996. In November 1999, the application date of this measure was retarded by 2 months (17 April 2000).
Canada announced the same decision in August 1999, although Quebec decided on a maximal stay of 1 month (instead of 6 months in other parts of North America).
Japan and New Zealand have also introduced "stays in the United Kingdom" as a blood donor exclusion criterion .

In Europe, according to information collected during meetings organised by the European Commission in October 1999 and February 2000 in which Member States' positions on this question were discussed, two Member States announced decisions. Austria has decided to exclude donors having spent more than 6 months in the United Kingdom, but this measure does not yet apply to donors of plasma for fractionation. Denmark has announced a decision not to make "stays in the United Kingdom" a blood donor exclusion criterion. In the other Member States, discussions on the appropriateness of such a measure continue. It is noteworthy that five European countries have now started routine leukodepletion of cellular LBP and that another three are intending to do so shortly.

The decisions taken by the United States and Canada should be seen in a context in which exposure of these countries' populations to BSE is very different from that of the French population. Indeed, in the absence of importations of British bovine products, the major source of exposure in these countries consists of stays in the United Kingdom. In the United States, routine leukodepletion of LBP has been recommended by experts, irrespective of possible nv-CJD transmission by blood, but this measure has not yet been universally adopted.

4-2 Discussion by the Committe for Proprietary Medicinal Products (CPMP) of the European Medicines Evaluation Agency (EMEA)

In July 1999, pending official implementation of the American decision, France approached the CPMP on this matter so that a European consensus could be reached, at least in the field of plasma-derived medicinal products, which are under the responsibility of the EMEA. This harmonisation was at least to cover the risk assessment, even if decisions and application of measures is up to each national authority.
To deal with this question, the CPMP organised a meeting of its expert group on TSE in December 1999. The group's principal conclusion was that precautionary measures should be envisaged to limit the risk of transmission by blood products. Nevertheless, before deciding on the appropriateness of excluding donors having stayed in the United Kingdom, it was necessary to determine the relative exposure to the BSE hazard of donors in each country and to assess the efficacy of alternative measures (leukodepletion, filtration and fractionation) on the risk of transmission by blood products.

5- Discussion on the impact of excluding donors having stayed in the United Kingdom

If such an exclusion measure were to be envisaged, the group underlined the importance of the following preliminary considerations:

- **the need to set the minimal duration of stay in the United Kingdom beyond which donors would be excluded.** In the current state of epidemiological data, this exclusion criterion cannot be correlated with a significant reduction in exposure to BSE, and the minimal duration of stay that could be adopted as the criterion for exclusion cannot currently be based on objective scientific arguments.

- **the need to evaluate the impact of this measure on national blood supply,** because exclusion of a given percentage of donors leads to the loss of a higher percentage of donations.

- **the need to take into account the consequences on the residual risk of HIV, HCV and HBV** linked to the rise in donations by first-time donors: J. Pillonel and A.M. Couroucé assessed the impact on the residual risk of HIV transmission of recruiting a supplementary percentage of first-time donors that would result from exclusion of donors having stayed in the United Kingdom.

  These residual risk estimates linked to donations made during the window period are based, for donations by repeat donors, on the Schreiber model (22) and, for donations by first-time donors, on the Janssen model (23). The estimates are based on the hypothesis that the incidence rate of HIV infection in donors remains stable whatever the percentage of supplementary first-time donors recruited.

  In the hypothesis in which all donors having stayed in the United Kingdom are excluded from donation (35%, cf. 2.3), the reduction in the number of donations by repeat donors would necessitate a 170% increase in the number of donations by first-time donors. The residual risk of HIV transmission would be increased by approximately 24%, raising from 5.6 to 6.9 the number of infectious donations collected during the window period and leading to one or two extra cases of post-transfusion HIV infection over a period 3 years. In the hypothesis in which 20% of donors are excluded (stays of more than 8 days), the residual risk would be increased by 14%, which would correspond to one extra case of post-transfusion HIV infection over a period 3 years.

  With HBV and HCV, these simulations are more difficult as there is no specific method to estimate the incidence of the two viruses in first-time donors.

  With HBV, however, a method developed by A.M. Couroucé, based on the identification of markers revealing recent infection, suggests that the impact would be very low.

  The impact would appear to be higher with HCV, roughly similar to that of HIV (25% rise in the residual risk if 35% of repeat donors are excluded), but the lack of a specific method makes the quantification of the rise in this risk more controversial.

- **the need for a coherent message to reassure persons concerned by this measure**, as well as their family and friends, especially regarding past and future stays in the United Kingdom. The message should take into account the French refusal to lift the embargo on British bovine product imports. The likely consequences of an exclusion measure of this type were discussed, and included the following:
  - the psychological impact on donors excluded by such a measure: they may be anxious, given that there is no test for the disease and the incubation period is potentially very long,
  - anxiety over children having stayed in the United Kingdom, and especially over future stays as long as France refuses to lift the embargo.

- **the need to define the position to be adopted towards this population**, designated as having increased exposure to the risk of developing nv-CJD, in other health areas (tissue, cell and organ donation; management of the nosocomial risk during treatment of these persons, e.g. dental care, ophthalmology, etc.)

- **the need for a preliminary feasibility study** to establish and validate the conditions in which the exclusion measure could be applied by the EFS and its consequences in terms of blood supply at the regional level, given the regional differences in the frequency of stays in the United Kingdom observed in the survey of 10 BTCs.
  It must also be recalled that if an exclusion measure were to be applied, it is likely that the percentage of first-time donors who would have to be recruited would exceed the percentage of donors excluded (as estimated by the survey). Indeed:
  - exclusion of a donor often leads to a loss of motivation among other donors who know the excluded donor well,
  - there is a risk of self-exclusion by some donors who will immediately consider themselves excluded because they have stayed in the United Kingdom, even if they do not meet the "length of stay" criterion,
  - first-time donors are usually recruited among young people, who themselves have a higher frequency of stays in the United Kingdom than older persons,
  - the percentage of donors excluded may rise with time, as young people have a higher frequency of stays in the United Kingdom (displacement to higher age groups).

- **the need for an analysis of the ethical and social consequences** of an exclusion measure of this type (DGS, Comité National Consultatif d'Ethique).

6- Summary and recommendations

6-1 Summary

To adapt health safety measures to newly available data, the AFSSaPS and AFS convened their experts in April, June and December 1999 and February 2000 to revise current measures concerning the risk of TSE transmission by labile blood products (LBP) and plasma-derived medicinal products (PDP).

The main question discussed at these meetings was the risk of transmission by blood products of new variant CJD (nv-CJD), a disease that would appear to result from transmission to humans of the agent responsible for bovine spongiform encephalopathy (BSE).

As regards "classical" CJD (sp-CJD), the experts consider that experimental and epidemiological information, and available follow-up data, suggest that the risk can be considered very low, or nil, meaning it is highly unlikely that any cases of sp-CJD transmission by blood or blood products will be observed. As a result, current precautionary measures should be revised (contraindications to donation, withdrawal of batches, information for prescribers and patients).

In contrast, the existence of a risk of nv-CJD transmission by blood products is compatible with the presence of the agent in lymphoid tissues, which in turn suggests its presence in blood. However, because of the recent emergence of nv-CJD and the long incubation period of TSEs, no experimental animal data or human epidemiological data are available to document possible transmission of the agent by blood products.

Analysis of exposure to the BSE hazard of blood donors in France shows that, on the basis of current data, the main source of exposure is consumption in France of bovine products imported from the United Kingdom rather than stays in the United Kingdom between 1980 and 1996. According to an analysis based on the most plausible hypothesis – that of dietary transmission of the BSE agent in the absence of other identified exposure factors – exclusion of all donors having stayed in the United Kingdom between 1980 and 1996, i.e. approximately 35% of donors, would only reduce total donor exposure to BSE by about 5%. This limited contribution of stays in the United Kingdom to global exposure to BSE is explained by the fact that consumption of British bovine products concerns the entire French population throughout the period concerned, even if dietary exposure to BSE in France is estimated to be 20-fold lower than in the United Kingdom, while stays in the United Kingdom concern only a third of the population and involve far shorter periods. Even if the hypotheses on which these estimations are based are incomplete, the analysis is compatible with the epidemiology of nv-CJD in France, the United Kingdom and the rest of the world.

This analysis shows that any measure aimed at excluding donors having stayed in the United Kingdom would only marginally reduce global donor exposure to BSE and, consequently, would at best have a limited impact on the potential risk of nv-CJD transmission by blood products.

While, by definition, donors having spent long periods in the United Kingdom are over-exposed, current epidemiological data do not allow this over-exposure to be correlated with a significant rise in the individual risk of developing nv-CJD. Thus, available data are inadequate to define the duration of stay beyond which over-exposure might become significant for a given individual, or to consider that over-exposure of persons having spent long periods in the United Kingdom is significant in terms of the risk for the community.

Given the global exposure to the BSE hazard and the limited efficacy of donor exclusion measures, the potential risk of nv-CJD transmission by blood products calls for an analysis of other measures -- already in place or applicable – potentially capable of reducing the risk. Currently, in the absence of validated screening tools for the infectious agent in blood, these measures are based on procedures used during blood product preparation.

Analysis of data on LBP leukodepletion and the manufacturing processes used for PDP shows that some processes already in place (e.g. leukodepletion and fractionation steps) contribute significantly to reducing the potential risk of nv-CJD transmission by blood products. The experts consider that these methods have a positive impact on blood product safety.

While the above analyses are agreed on by most of the group, one expert wishes the following points, which have already been discussed by the group and included among the factors to be taken into account, to be restated here:

- although donors having spent long periods in the United Kingdom make only a small contribution to global donor exposure to BSE, they have individual over-exposure which, according to the working hypotheses chosen, may be up to 7 times higher than that of persons who have never been in the United Kingdom,
- the effectiveness of LBP and PDP preparation processes in terms of the reduction in the infectivity of the resulting products is not sufficiently documented; reduction factors must be validated product by product,
- depending on the blood product considered (LBP, PDP, etc.), options such as exclusion of donors having stayed in the United Kingdom or non fractionation of plasma collected in France, together with other technological improvements in manufacturing processes, should also be envisaged in deciding how to manage this risk.

Finally, two experts recalled that the estimation of exposure described in section 2 suggests that the French population was globally exposed to BSE through imported British bovine products and that French blood donations could present a specific "geographic" risk potentially facilitating adaptation of the nv-CJD agent and inter-human transmission which, especially during medical procedures, could prove difficult to control.

In conclusion, in the opinion of most of the experts, considering the global exposure of the French donor population to the BSE hazard, and given that donor exclusion measures would, at best, have a limited impact on exposure, the measures that currently appear most effective on the potential risk of nv-CJD transmission by blood products are those that reduce infectious load during preparation of these products.

6-2 Recommendations

On the basis of this report, the expert group makes the following recommendations:

- **Reinforce measures potentially reducing the infectious load**, such as plasma leukodepletion, in addition to leukodepletion of cellular LBP (applied since April 1998), and the addition of a nanofiltration step during the manufacturing of some plasma-derived medicinal products;
- **Continue the validation of processes reducing the infectious load** during the preparation of both LBP and PDP.
- **Maintain close scientific and epidemiological surveillance** in order to assess all new data likely to affect the current risk analysis, including data that would call into question the different sources of exposure of the French population to the BSE agent. Particular attention should be paid to the following:
  - ➢ studies on infectivity of blood from patients with nv-CJD
  - ➢ results from the on-going bovine-bovine transmission studies,
  - ➢ studies on nv-CJD transmission to primates and transgenic mice
  - ➢ development of detection tests for PrPres that would allow the incidence of the infection in the population to be determined, with possible application to donor selection. It should be noted that these tests will not be available for several years.
- The following actions:
  - ➢ review of current precautionary measures regarding the risk of classical TSE (exclusion criteria to donation, withdrawal of products, information for prescribers and patients)
  - ➢ assessment of the risk-benefit ratio of other biological products of human origin, especially tissues and organs, that could be imported from the United Kingdom
  - ➢ information for prescribers on the risk-benefit ratio of non leukodepleted LBP used in pretransplant transfusion programmes
  - ➢ epidemiological survey on dietary habits and stays in the United Kingdom by European populations. Such data would be useful to determine exposure to BSE and to determine the relationship between exposure and the incidence of nv-CJD.

If a decision is made to exclude donors having spent long periods in the United Kingdom during the period most at risk, the expert group underlines the need to precede this decision by a certain number of actions listed in section 5, principally:

- an assessment of the quantifiable impact of the measure on residual risks (HIV, HBV and HCV) linked to the rise in donations by first time donors, depending on the chosen exclusion criterion.
- analysis of the ethical and social consequences of an exclusion measure of this type (DGS, Comité National Consultatif d'Ethique)
- setting up a coherent information campaign to explain the exclusion measure, to reassure the persons concerned (and their family and friends), and to determine how to manage this

population, designated as being at an increased risk of developing nv-CJD, in other health areas.

- feasibility study to validate the conditions of application of the exclusion measure by the EFS and its consequences in terms of blood supply at the regional level, before setting a date on which the measure would be adopted by all BTC.
- concertation with other European Union Member States, the European Commission, and EMEA.

****

References

1- Note AFS-97103 du 22 octobre 1997: Actualisation des contre-indications au don à l'égard du risque possible de transmission des ESST par les produits sanguins labiles.

2- Note AFS-9758 du 30 mai 1997: Mesure d'ajournement définitif du don des receveurs de produits biologiques d'origine humaine non sécurisés.

3- Proceedings of the meeting of the Transmissible Spongiform Encephalopathies Advisory Committee 2 June 1999. DHHS PHS- FDA.

4- Press release, Ministery of Health, 18 August 1999

5- A.F. Hill et al. Investigation of variant Creutzfledt-Jakob disease and other human prion diseases with tonsil biopsy samples. Lancet,1999, 353, 1983-189.

6- J. Willesmith, Communication to the EU TSE committee, 1999

7- P. Brown et al. Further studies of blood infectivity in an experimental model of transmissible spongiform encephalopathy with an explanation of why blood components do not transmit CJD in humans. Transfusion, 1999, 39, 1169-1178.

8- Opinion on the risk quantification for CJD transmission via substances of human origin. Scientific Committee on Medicinal products and medical devices, European Commission, DG XXIV, October 1998

9- M.J. Schmerr et al. Use of capillary electrophoresis and fluorescent labeled peptides to detect the abnormal prion protein in the blood of animals that are infected with a transmissible spongiform encephalopathy. J. Chromatogr. A 853, 1999, 207-214.

10- R.G. Rohwer: Communication personnelle, 1999.

11- D. Dormont. Le risque de transmission sanguine des agents transmissibles non conventionnels ou prions. Xème colloque de virologie de Versailles le Chesnay, 1996, 21-33.

12a- T.F.G. Esmonde et al., Creutzfeldt-Jakob disease and blood transfusion. Lancet, 1993, 341, 205-207.

12b- N. Heye et al., Creutzfeldt-Jakob disease and blood transfusion. Lancet, 1994, 343, 298-299.

13- B. Evatt et al. Surveillance for Creutzfeldt-Jakob disease among persons with hemophilia. Transfusion, 1998, 38, 817-820.

14- C. van Duijn et al. Case-control study of risk factors of Creutzfeldt-Jakob disease in Europe during 1993-95. Lancet, 1998, 351, 1081-85.

15- S. Collins et al. Surgical treatment and risk of sporadic CJD: a case control study. The Lancet, 1999, 353,693-697.

16- MR Scott et al., Compelling transgenetic evidence for transmission of bovine spongiform encephalopathy prions to humans, PNAS, 1999, 96, 15137-15142.

17- J. Collinge et al. Molecular analysis of prion strain variation and the aethiology of " new variant CJD. Nature, 1996, 383, 685-690.

18- M.E. Bruce et al. Transmissions to mice indicate that " new variant " CJD is caused by the BSE agent. Nature, 1997, 389, 498-501.

19- K. Birchard. Variant CJD found in Ireland. Lancet, 1999, 353,2221.

20- J. Tateishi et al., Removal of causative agent of Creutzfeldt-Jakob disease (CJD) through membrane filtration method. Membrane, 1993, 18 (6), 357-362.

21- Oral communications and poster presentations at various meetings: Dr. Sato: Francfort 1997, Mac Lean 1998; Dr. Morgenthaler: Lisboa 1998; Dr. Rohwer: Washington 1999; Dr. Foster: Edinburgh 1999; Dr. Petteway: London 1998 and1999.

22- G.B. Schreiber et al. The risk of transfusion-transmitted viral infections. N. Engl. J. Med.,1996, 334, 1685-90.

23- R.S. Janssen et al. New testing strategy to detect early HIV-1 infection for use in incidence estimates and clinical and prevention purposes. JAMA, 1998, 280, 42-48.